

REVIEW ARTICLE

Allergy and sports in children

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Abstract

Physical activity is beneficial for children with positive outcomes for mental and physical well-being. Allergic conditions unique to the sporting arena may serve as an impediment to participation in physical activity for allergic children. A common example is exercise-induced asthma; less common activity-related allergic conditions include food-dependent exercise-induced anaphylaxis, exercise-induced anaphylaxis, and exercise-induced urticaria. Allergic children may also be at risk of allergic reactions when exposed to allergens that are more commonly found in the sports environment, e.g., latex, sports drinks, and medications such as NSAIDs. Recent advances in our understanding of the patho-physiological and immunologic mechanisms that may account for these conditions have facilitated more effective and safer management strategies. There are also important immunologic lessons to be learnt with respect to specific physical factors that may result in diminished allergen tolerance; indeed, these lessons may facilitate safer allergen desensitisation regimens. The role of the immune system in exercise-induced immunoallergic syndromes, clinical aspects, and diagnostic and therapeutic approaches are discussed in this review.

Physical activity is fundamental for children, for their growth and long-term development (1). It has been shown to induce positive physiological and psychological effects, an improvement of cardiovascular, respiratory, and muscular systems. Furthermore, children undertaking physical training frequently modify their diet, with a reduced risk of overweight and obesity; in so doing, physical inactivity is considered to be an independent risk factor for various chronic diseases of adulthood (2). Through the psycho-neuro-immune network, physical activity can influence nervous, endocrine, and immune systems and this may result in a Th-2 polarization with a worsening of allergic symptoms or exercise-related allergic syndromes for some of the over 25% of amateur and professional athletes affected by allergic diseases (3); in contrast, regular physical activity may induce beneficial immune system changes with a reduction in pro-inflammatory cytokines and a switch toward a Th-1 profile, thereby reducing

the allergic inflammation. Such changes will depend on the intensity, duration, and type of the exercise itself (4). It is reassuring that many allergic athletes successfully compete at the highest levels; it, therefore, remains the goal of the allergist to facilitate optimal performance through correct diagnosis and management of sports-related allergic conditions.

Exercise, immune system, and inflammation

Both innate and acquired immunity are influenced by exercise, and increased or reduced susceptibility to infections, in particular to upper respiratory tract infections (URTI), may be a result of these modifications. Studies performed to date in the field of 'exercise immunology' are subject to many variables; these include 'acute' vs. 'prolonged' exercise, different sports, variable ages, recreational vs. professional athletes, and different immunologic methods.

'Acute' exercise and immune changes

'Acute' exercise (i.e., a short bout of intense physical activity) is associated with changes in mononuclear blood cells (MBC): a neutrophilia is rapidly noted, which continues to increase after exercise; their oxidative burst and degranulation in response to bacterial stimulation are however reduced, an effect which can last for several hours (5, 6). Monocytosis occurs during acute exercise, probably representing a shift from the marginated to the circulating monocytes pool (7). Macrophage antigen-presenting ability is reduced after exhaustive acute exercise (8).

Natural killer (NK) cells, the most responsive immune cells to acute exercise, show a striking exercise-induced increase, whereas their cell count drops after exercise to below than half the normal level. Their cytotoxicity increases during exercise but it is depressed after exercise, probably increasing susceptibility to infections (9–11).

Similar changes are noted for T and B cells, i.e., an increase in T and B cells during exercise; these changes are directly proportional to the exercise intensity. A notable drop to below-normal values occurs post-exercise prior to a return to the pre-exercise values over 24 h; this effect may be prolonged if the interval between two exercise sessions is too short (12, 13).

It is worth noting that the MBC changes occurring during 'acute' exercise arise through acute immune stressors, e.g., catecholamine-mediated redistribution. If such changes are sufficient to influence susceptibility to disease as seen after heavy exercise remains controversial (14).

Levels of salivary IgA, an important marker of mucosal immunity, are not altered by short, intensive bouts of exercise (15).

Little information is available on dendritic cells, despite their important emerging role; some animal studies demonstrate an increase after exercise (16), and further studies are needed to better understand their role in exercise immunology.

Exercise training (regular exercise) and immune changes

Physically active people show a lower monocyte inflammatory response to LPS and a lower percentage of CD14+/CD16+ cells. Some studies report a reduction in neutrophils count in patients with chronic inflammatory conditions, supporting the 'anti-inflammatory' theory about the regular exercise effects (4, 17).

As regards NKs, several studies on animals and humans reported increased cytotoxicity after moderate exercise training in sedentary subjects and their increase in absolute number and percentage after a 1-yr systematic training in professional football players (4 and SR Del Giacco et al., submitted). Salivary IgA do not show changes with regular, moderate exercise, but may decrease during periods of prolonged, intensive training. Some authors describe a negative relationship between this reduction and the risk of URTI, the main cause for asthma exacerbations in children (15, 18).

Inflammation

The important pathogenic role of inflammation in exercise-induced asthma (EIA) has put the airway epithelium into the focus of several researchers. Exercise may prime airway inflammation, and repeated hyperventilation challenges may cause epithelial damage and increased peptidoleukotriene concentrations in bronchoalveolar lavage (BAL) fluid (19). In cultured human bronchial epithelial cells, exposure to a hyperosmolar medium or the cooling-rewarming process is capable of triggering a complex inflammatory cascade with increased expression of chemokines, such as IL-8 and RANTES (11, 20). Increased numbers of inflammatory cells are found in bronchial biopsies, BAL fluid, or induced sputum of athletes from different sports measured at rest (21). Swimmers, in particular, show a marked sputum eosinophilia (up to 38%). It should be noted that this eosinophilia is reversible after stopping active sport; this raises the hypothesis of an 'athletes' asthma' for which the major risk factor is the sport practice itself (22, 23). Some authors hypothesize a role also for the vascular endothelial growth factor (VEGF), responsible for the microvascular remodeling at the airways' epithelium level (24) and for endothelin-1 in EIA (25).

Furthermore, in general, pro-inflammatory cytokines (IL-1, IL-6, TNF- α) are increased after prolonged strenuous exercise (11), but recent findings are resulting in interesting new theories on the anti-inflammatory effect of regular, moderate exercise. Several studies reported lower levels of Th-2 cytokines and enhanced Th-1 and T-reg responses in murine models of asthma performing aerobic exercise vs. sedentary mice (26–28). Preliminary data in adult humans confirm these data (SR Del Giacco et al., submitted).

It is important to mention that a relatively low number of studies have investigated immune response in children, mainly due to ethical limitations. When unavailable for children, some of the findings listed are transferred from an adult population.

Allergy and exercise

Exercise may trigger allergic respiratory, systemic, and cutaneous disorders: EIA, exercise-induced anaphylaxis (EIA), and exercise-induced urticaria (EIU) are the most common.

Exercise-induced asthma and other exercise-induced respiratory problems in children

Physical activity and asthma

In asthmatic children, physical fitness has been related to psychological functioning. EIA frequently occurs in childhood asthma. In an Oslo birth cohort, exercise-induced bronchoconstriction (EIB) was found in 8.6% of all 10-yr-old children and in 36.7% of children with current asthma (29).

When participating in systematic physical training, the asthmatic adolescent or child improves fitness and quality of life as confirmed by a Cochrane-based meta-analysis of eight training studies, including 226 asthmatics from 6 yr of age

(30). Counil et al. confirmed improvement in aerobic and anaerobic fitness in asthmatic adolescents (mean age 13 yr), but no improvement in lung function after 6-wk training with high intensive bouts (31).

There are studies demonstrating that asthmatic children are as physically fit and as physically active as healthy children (32), whereas other studies have demonstrated that physical activity and fitness are related to asthma control and improves with optimal treatment and asthma control (33). However, parents of 10–15 yr-old tend to underestimate the burden of asthma experienced by their children, especially the effects on physical activity (34). Therefore, mastering EIA is considered one of the main objectives of treating childhood asthma.

Mechanisms of exercise-induced asthma

Ventilation increases markedly during physical activity, leading to increased water loss and heat loss through respiration. Cooling of the airways results in smooth muscle contraction and mucosal edema in susceptible individuals through reflex parasympathetic nerve stimulation and autoregulation of the bronchial circulation (35). However, increased water loss increases the osmolality of the extracellular fluid of the bronchial mucosa, causing water to move extracellular with increasing intracellular ion concentration (36). This may cause mediator release: both newly formed eicosanoids and preformed mediators like histamine causing bronchoconstriction. EIA occurs usually shortly after heavy exercise and not during maximum exercise intensity.

Diagnosis of exercise-induced asthma

Exercise-induced asthma can be diagnosed by standardized exercise test with high exercise load, up to 95% of maximum exercise load and standardized as regards environmental temperature and humidity (37). Any type of exercise can be used, but running is often preferred. The children/adolescents run on a treadmill with an inclination of 5.5% (3°) with increasing exercise load over 2 min then keeping an exercise load assessed by a heart rate of 95% of maximum for another 4 min. FEV1 is determined before and after running and 3, 6, 10, and 15 min thereafter. A reduction in FEV1 of $\geq 10\%$, from before to after exercise demonstrates EIB.

The exercise test has high specificity for the diagnosis of asthma, but lower sensitivity, especially when the children are treated with inhaled steroids. The exercise test is a useful measure of how well the asthmatic child masters physical activity. Inhalation of mannitol has been suggested as a substitute measure for EIB (38). The mannitol test gives information about the indirect bronchial responsiveness comparable to EIB, but not about physical fitness, motor skills, and motor development as the exercise test does.

Other measures of bronchial responsiveness, direct or indirect, like responsiveness to inhaled metacholine and the eucapnic voluntary hyperventilation test, also give important information about asthma severity, but are not diagnostic for

EIA. These tests are much used to assess asthma in athletes and to document the athletes' need for asthma medication.

Differential diagnosis and other exercise-induced respiratory disorders

Exercise-induced asthma is characterized by expiratory dyspnoea shortly after a heavy exercise. If the respiratory distress occurs during maximum exercise and is inspiratory, exercise-induced vocal cord dysfunction (VCD) is a more probable diagnosis, first described in a young girl by Refsum (39). Among well-trained children, and especially girls, this occurs as frequently as EIA. This differential diagnosis is very important, as asthma treatment has no effect upon this condition. EIA may coexist with VCD. The following definition has been proposed for VCD: an intermittent extra thoracic airway obstruction occurring mainly during inspiration, leading to dyspnoea of varying intensity (40). Exercise-induced VCD should be suspected with inspiratory respiratory stridor during maximum exercise intensity. A maximum intensity treadmill run, when audible inspiratory stridor occurs during maximum intensity, can confirm the diagnosis. The diagnosis is further verified by continuous laryngoscopic exercise test (41).

Also, exercise-induced hyperventilation with increased end-tidal CO_2 at the end of exercise is a differential diagnosis to EIA, as are poor physical fitness and obesity in the common asthmatic patient, but rarely in physically trained asthmatic children. Chronic heart disease may reduce exercise tolerance.

In adolescent athletes, there are also some other differential diagnoses to EIA, like exercise-induced arterial hypoxemia and swimming-induced pulmonary edema, but these are rare in children not active in sports (see Table 1 for listing of differential diagnoses for exercise-induced respiratory problems in adolescents).

Treatment of exercise-induced asthma

Early diagnosis of EIA is important for the start of optimal treatment. The aim is that asthmatic children should be able to participate in physical activity and sports on an equal level with their healthy peers.

Optimal control of EIA is most often obtained by anti-inflammatory treatment through inhaled steroids. The dose may vary according to asthma severity, but the effect occurs quickly beginning after 1 wk's treatment and improving further through the following weeks (42). Additional control of EIA may be obtained by pre-treatment before physical activity with bronchodilators like inhaled β_2 -agonists, short- or long-acting (43), or ipratropium bromide (44). Also, leukotriene antagonists may improve control of EIA. In severe asthma, a fixed combination of inhaled steroid and long-acting β_2 -agonists may increase control, especially in older children. However, one should be aware of the tolerance development of EIA by regular use of long-acting β_2 -agonists.

A novel inhaled steroid, ciclesonide, may be of particular interest to athletes (45). This steroid is a pro-drug, being activated in the bronchial epithelium, and when passing into the

Table 1 Exercise-induced asthma: differential diagnosis

Diagnosis	Relevant for	Clinical presentation	Verification of diagnosis
Exercise-induced asthma	Asthmatic children and children active in sports	Symptoms occur shortly after (sometimes during) physical exercise. The dyspnea is of expiratory type. By auscultation: Rhonchi and sibilating rhonchi. Respiratory retractions. Gradual improvement either spontaneously or after inhaled bronchodilator	Exercise test with sub-maximal exercise load (95% load). Spirometry before and after exercise
Exercise-induced vocal cord dysfunction	Asthmatic children and children active in sports	Symptoms occur during maximum exertion. Symptoms disappear when exercise is stopped unless the patient continues to hyperventilate. The dyspnea is of inspiratory type. There are audible inspiratory sounds from the laryngeal area and no signs of bronchial obstruction. No effect of pre-treatment with inhaled bronchodilator	Exercise test with maximal exercise load, 6–8 min duration Direct laryngoscopy during exercise test.
Exercise-induced hyperventilation	Children and adolescents active in sports, Children in general	Hyperventilation with respiratory dyspnea and increased end-tidal CO ₂	Case history, observation during dyspnea
Exercise-induced arterial hypoxemia (EIAH)	Children and adolescents active in sports	Occurs in well-trained athletes with high maximum oxygen uptake. Thought to be due to diffusion limitations and ventilation-perfusion inequality. Incomplete diffusion in the healthy lung may be due to a rapid red blood cell transit time through the pulmonary capillaries	Exercise test, sub-maximal to maximal level
Swimming-induced pulmonary oedema (SIPE)	Children and adolescents active in sports	May occur after heavy swimming exercises with symptoms of hemoptysis, cough, and respiratory distress. Reduced diffusion capacity (TLCO) for up to weeks afterwards	Case history, clinical examination, and lung function measurements during an active episode
Other chronic lung diseases	Children with chronic lung disease	Reduced baseline lung function may reduce physical performance due to limitations in airflow and lung volumes	Exercise test with measurement of tidal flow volume loops during exercise
Other general disease	Children with chronic illnesses	Chronic heart diseases and others general disorders	General diagnostic workout
Poor physical fitness including obesity	Children in general	Related to expectations. High heart rate after low-grade exercise load	Exercise test: Assessment of physical fitness by determination of $\dot{V}O_{2max}$ or maximal exercise load

blood stream will be protein bound and inactivated rapidly. The side effects of this drug are thus minimal, both as regards oral candidiasis and hoarseness as well as potential suppression of the adrenals. This makes ciclesonide of particular interest for athletes, being dependent upon an optimal stress response from the adrenals.

Asthma and sports in children and adolescents

The development of asthma in previously healthy endurance athletes is another aspect of asthma and sports. This asthma phenotype differs from the common asthma phenotypes in childhood and is characterized by cough, phlegm, increased bronchial secretions, and viral exacerbations. It is also characterized by exacerbations caused by repetitive exhaustive physical exercises, such as many closely placed competitions during championships. This phenotype develops after years of intensive training within endurance sports, most often in cross-country skiers and swimmers. The causative pathogenic mechanisms are thought to be airway's epithelial damage owing to regularly repeated increased ventilation during training and competition, usually combined with exposure to an environmental agent, like cold air inhalation for cross-country skiers, and organic chlorine products for competitive swimmers (46). It has been reported that mechanisms may involve epithelial damage (47), disturbed repair owing to the regularly occurring trauma to the airways, following airways inflammation and an increased parasympathetic activity in the airways (44).

This development usually occurs gradually over several years and is therefore not that common in childhood and adolescence. However, for some types of sport, the environmental exposure is so strong that it may develop early during the athletic career. One such example is competitive swimmers who very frequently have already developed bronchial hyperresponsiveness during their teens (48).

Treatment for asthma in adolescent athletes

For athletes with asthma, anti-inflammatory treatment by inhaled steroids is most important, both to reduce inflammation and the clinical impact of repeated training and competitions and to possibly improve long-term prognosis. The treatment should follow regular treatment guidelines. Bronchodilators are frequently needed both as pre-treatment before competitions and to reduce symptoms. Experience shows that inhaled ipratropium bromide is frequently an effective bronchodilator. Inhaled β_2 -agonists, both short- and long-acting are often needed. It is important to assess objective measures like lung function and bronchial hyperresponsiveness when treating competitive athletes, as symptoms are frequently reported without clinical correlate.

For many years, there have been strict regulations for the use of asthma drugs in sports. Initially, one feared that these drugs might improve performance, but now it is generally accepted that inhaled steroids and inhaled β_2 -agonists do not improve performance, and the regulations have been loosened for some drugs, but not all. At present, there are no

restrictions for the use of inhaled steroids, inhaled ipratropium bromide, leukotriene antagonists, and the inhaled β_2 -agonists salbutamol, salmeterol and formoterol. Still, inhaled terbutaline is restricted in competitive sports, and objective measurements of bronchial hyperresponsiveness, EIB, or bronchodilator reversibility must be documented for the approval for its use. It is important that physicians treating children and adolescents with asthma who are also active in competitive sports keep updated on the doping rules, follow these in the selection of drugs and give the necessary documentation for the sports authorities.

Nutritional factors may also be of importance in EIA management: a recent study (49) shows an inverse relationship between level of adherence to the Mediterranean diet and prevalence of exercise wheeze in school-aged children. Unstructured dietary patterns leave a large room for improvement of the diet in asthmatic children and adolescents (50).

Exercise-induced anaphylaxis and other skin syndromes

Exercise-induced anaphylaxis

Exercise is a common cofactor in anaphylaxis; indeed, some 2–15% of anaphylactic episodes are caused by or are associated with exercise (51, 52). Exercise may also be the primary trigger for anaphylaxis – a condition known as exercise-induced anaphylaxis (EIAN). EIAN is a rare, unpredictable, and potentially life-threatening syndrome characterized by anaphylaxis associated with exercise or lesser physical activities of varying time frames and intensities. EIAN may occur independently of food allergen ingestion or may require the ingestion of a food allergen before or shortly after exercise, known as food-dependent exercise-induced anaphylaxis (FDEIAN). It has been described that FDEIAN may even occur if the food trigger is ingested soon after exercise (53, 54). In FDEIAN, both the food allergen and exercise are independently tolerated. Additional cofactors may be required to induce anaphylaxis, e.g., medication intake, known as 'summation anaphylaxis' (see Table 2). Given the rarity of this condition, knowledge in this field is predominantly based on case reports and reviews (54–58).

Pathophysiology

Many hypotheses have been proposed with respect to the pathophysiological mechanisms that underlie EIAN and FDEIAN. Each of these hypotheses was recently considered in the context of advances in our understanding of exercise physiology by Robson-Ansley and Du Toit (56). The authors stress the observation that EIAN is generally reported following sub-maximal exercise of a relatively short duration; this fact alone eliminates the majority of the proposed pathophysiological mechanisms as significant physiological changes in blood pH, and osmolality, do not occur at sub-maximal levels of physical activity: they postulate that exercise, even of a short duration, results in significant redistribution of blood

from the gut (where mucosal mast cells are by default tolerant to allergenic peptides) to other locations such as the skin or skeletal muscle where 'gut-tolerated' peptides are redistributed to sensitized 'phenotypically different' mast cells inducing either a transient loss of tolerance or an amplification of low-grade allergy, thus presenting with EIAN (56). An appraisal of these hypotheses is summarized in Table 2. Regardless of the mechanism, allergists have long been aware of these exercise-associated immune changes. For example, patients undergoing venom or pollen immunotherapy are routinely advised to refrain from exercise in the immediate time interval after administration. Similar findings are emerging from the many oral tolerance induction studies that are underway; here 'hard won' gains in allergen thresholds may unexpectedly be compromised possibly due to 'immune insults' secondary to infection, sleep disturbance, menstruation, and exercise (59, 60).

Key clinical features

The symptoms of FDEIAN vary in severity; fatalities have however not been reported. EIAN occurs in all ages, in both sexes, and is more common in atopic individuals. EIAN has been described in high-performance athletes and in individuals undertaking only occasional exercise. Even sub-maximal physical activity, for example, raking garden leaves, has been reported as a trigger for EIAN (57). There is no one consistent 'exercise-associated factor,' e.g., ambient temperature, humidity, anticipation (i.e., planned vs. spontaneous activity). Although wheat is the most commonly reported food allergen associated with FDEIAN, many other food allergens have also been reported. It is important to consider the role of food allergies that may be associated with food allergens peculiar to exercise, e.g., commercial rehydration fluids, such as soya and animal-derived gelatine, omega-5-gliadin in carbohydrate meals eaten for 'carbo loading,' nut protein in massage oils. Recent advances in our understanding of allergic reactions to mammalian sugars (oligosaccharide galactose alpha-1, 3-galactose) are interesting as here too there is a link to exercise as a cofactor in some case reports; these reactions may occur some hours after ingestion, which is atypical for IgE-mediated food-induced allergic reactions (71). The natural history of EIAN is not well described but opinion is that with careful management, a gradual return to exercise can be safely achieved for most patients.

Diagnosis and differential diagnoses

Exercise-induced anaphylaxis is primarily a clinical diagnosis; when symptoms and signs are not typical, care should be taken to work through the broad list of differential diagnoses of conditions that may be associated with exercise (see Table 3). The clinician needs to consider not only those diagnoses that are 'exercise-induced' but also 'exercise-related' allergens; additional examples include allergy to medications, joint supports and strapping, and latex allergy. Because of its unique properties, latex is still commonly found in sports equipment such as basketballs and tennis racket hand grips. Allergic reactions to non-steroidal anti-inflammatory agents,

which are frequently ingested by athletes, such as ibuprofen, should always be considered as should use of legal and illegal performance enhancers, e.g., creatine, chondroitin, erythropoietin, and steroids. Investigations will include skin prick testing and the determination of specific immunoglobulin E (Sp-IgE) testing. Broad allergen screening panels may be required so as not to miss 'less typical' food allergens, e.g., lupine. Measurement of specific IgE to omega-5 gliadin performs well in the detection of wheat-induced FDEIAN and may detect cases that would otherwise be missed using standard wheat allergy tests (skin prick test and specific IgE) (68, 72). Serial tryptase levels are of use if raised but are seldom practical in the acute EIAN setting. A diagnosis of food-independent EIAN can only be made once FDEIAN has been excluded; to do so, the clinician will need to rely on a thorough clinical history and modified exercise challenge tests (with and without food). Use of such tests is previously highlighted. A diagnosis of EIA will require consideration for patients who experience obstructive respiratory symptoms (in the absence of allergic manifestations such as hives or angioedema).

Management

As physical activity cannot be avoided, or even scheduled in young children, supervised modified exercise challenge tests are indicated (unless the clinical history is unequivocal) to safely establish a diagnosis of EIAN. If food plays a role in the presentation, then dietary management is required; this is best achieved with the help of a dietician. A personalized emergency plan and medications are required but should only be issued after the individual (and family/carers) has been trained in the identification and treatment for anaphylaxis. A slow, supervised return to exercise should be encouraged. If a diagnosis of FDEIAN has been made, then the allergen should be avoided both prior to and after exercise. A 3-h avoidance of the allergen prior to planned exercise and 1 h following exercise has been proposed (56): the rationale for this is twofold. Firstly, one study indicates that in patients with FDEIAN, the interval between food ingestion and EIAN ranged from 1 to 3 h. Secondly, avoiding food ingestion until 1 h post-exercise will permit the recovery of blood flow following exercise to pre-exercise distribution as discussed previously. To achieve this, it may be necessary to totally eliminate the food from the diet of athletes and physically active young children. The role of prophylactic antihistamines, anti-leukotriene antagonists, and oral steroids, which is well documented for use in EIA, has not been well studied for the control and prevention of EIAN. It also seems prudent for food allergic individuals to avoid aspirin or any medication/therapy/alcohol, as this may alter gastrointestinal integrity prior to exercise.

Rashes associated with exercise

There are many non-IgE-mediated rashes that occur in association with exercise the commonest of which is physiological flushing. Cholinergic urticaria is one of the physical urticaria variants for which there are many physical triggers. Common physical triggers (associated with exercise) include one or

Table 2 Appraisal of hypotheses of the patho-physiological mechanisms that underlie EIA/n

Contemporary hypotheses for EIA/n	Physiological basis of hypotheses	Exercise physiology in context of EIA/n	Likelihood of occurrence in context of EIA/n. Future research direction
Changes in plasma osmolality during exercise increase basophil histamine release. 340 mOsm associated with increase in basophil histamine release in FDEIA/n ($n = 1$) (61)	Exercise can increase plasma osmolality. Dramatic changes in osmolality can alter basophil histamine release (61)	Plasma osmolality is relatively stable during short-term, low intensity exercise. 5% loss of body mass through dehydration required to achieve osmolality of 305 mOsm (62)	Unlikely Effect of minor shifts in osmolality on basophil degranulation warrants further investigation
Increased acidity in blood results in increased mast cell degranulation as shown by protective effect of sodium bicarbonate in FDEIA/n during exercise (63)	Exercise induces metabolic/lactic acidosis. pH 7 provides optimal conditions for mast cell degranulation (64)	Supramaximal exercise associated with lactic acidosis (65). Acidosis is unlikely to occur in the context of EIA/n	Possible Changes in muscle pH greater than blood, prophylactic effect of sodium bicarbonate warrants further investigation
Increased exercise-induced gut permeability (GI) results in appearance of gliadin peptides in WDEIA (66)	Exercise can increase GI and potentially increase the absorption of allergenic peptides	Only very prolonged exercise is associated with increases in GI. Exercise for 90 min at 70% $\dot{V}O_{2\max}$ increase GI (67). Increased GI is unlikely to occur in the context of EIA/n	Unlikely Caution: aspirin, NSAIDs, alcohol ingested can increase GI permeability during or prior to exercise
Exercise-induced increases in tissue transglutaminase (tTG) activity results in post-digestion allergenic peptide aggregation (68)	tTG activity increase by severe homeostatic disruption and associated increase in inflammatory cytokine, free radicals, and cortisol release. Dysregulated tTG results in fibrosis, autoimmune disorders	Short-term, low intensity exercise results in slight, transient increase in inflammatory cytokines, free radicals, or cortisol (4) No evidence of tTG/allergen complexes in circulation in EIA/n	Unlikely Determination of lowest concentration of cytokines to increase tTG required
Redistribution of blood flow from viscera to active tissues results in exposure of allergen to phenotypically different mast cells (56)	Exercise results in altered blood flow from the viscera to the active tissues. Mast cell heterogeneity has been demonstrated in a number of tissues in humans (69)	Mild to severe exercise alters blood flow distribution with greater percentage of cardiac output going to active tissues and reduction to viscera (70)	Possible Hypothesis warrants further investigation in EIA/n patients vs. healthy controls

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EIA/n, exercise-induced anaphylaxis; FDEIA/n, food-dependent exercise-induced anaphylaxis.

Table 3 Exercise-induced anaphylaxis – differential diagnoses

Swelling/angioedema	Chronic urticaria and angioedema ACEI medication intake Complement deficiency/dysfunction
Cutaneous/Flushing	Cholinergic urticaria Physical urticaria secondary to pressure, vibration, sunlight, sweat Physiological flushing Scombroid fish poisoning Mastocytosis Rare – Peptide-secreting tumours (carcinoid, VIP'oms). Medullary carcinoma of thyroid, or pheochromocytoma
Neurological	Epileptic seizure Vasovagal episodes
Vascular	Cardiac abnormalities, e.g., arrhythmias Vasovagal episodes Systemic inflammatory syndromes
Upper airway symptoms	Vocal cord dysfunction Panic disorders
Lower airway symptoms	Exercise-induced asthma

more of the following: sweat, temperature change, alterations in blood flow, and emotional strain (73). The underlying patho-physiological mechanism remains incompletely understood. Onset is usually in older children entering their second decade of life, and the diagnosis is more common among females. The typical clinical appearance is that of small (2–4 mm) wheals surrounded by large areas of erythema. Systemic involvement, although uncommon, may occur. Attacks often subside with rapid cooling, and a refractory period may be experienced after an attack (this represents an opportunity for the development of training strategies for the affected athlete). Delayed pressure urticaria (with or without angioedema) is a particularly distressing condition, in which painful deep tissue swelling occurs several hours after a sustained pressure stimulus, e.g., wearing a mouth guard, prolonged grip of sports equipment, on the soles after running, or the buttocks after long distance cycling or rowing. A variable,

typically poor, therapeutic response is achieved with antihistamines alone. Solar urticaria occurs in otherwise healthy individuals soon after sun exposure. The management includes barrier protection, use of sunscreens, and antihistamines before sun exposure. Tanning can lessen the reaction to sunlight. Aquagenic urticaria is uncommon and represents a reaction of the body to water; this is independent of temperature. Cold urticaria is a particular management challenge; patients typically experience severe urticaria in the distribution of cold exposure; anaphylaxis has been associated. A personalized emergency plan that includes adrenaline is indicated. Cold urticaria and cholinergic urticaria may coexist in the same patient. Other sports-related rashes may arise through contact dermatitis with allergens unique to the sports environment, e.g., resins in swimming goggles or gymnast chalk/dust, chemical substances contained in wet suits or in athletic equipment or even pruritic dermatitis owing to parasites larvae ('sea bather's eruption') (11).

Concluding remarks

There are many sports-related allergic conditions that may affect children participating in sport; given the many benefits of sport for children, it remains a priority to correctly identify and manage any such conditions. Recent advances in our immunologic and clinical understanding of these conditions have facilitated more effective, and safer, training, and therapeutic strategies. There is however still much to learn with respect to the pathophysiology of these conditions. It is the role of cytokines, psycho-neuro-immune pathways, and underlying genetic susceptibilities that are receiving the greatest attention in the field of exercise immunology. A challenging task is for researchers to marry up any changes found with the many variables unique to both children and sport.

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References

- Scheett TP, Nemet D, Stoppani J, Maresh CM, Newcomb R, Cooper DM. The effect of endurance-type exercise training on growth mediators and inflammatory cytokines in pre-pubertal and early pubertal males. *Pediatr Res* 2002; **52**: 491–7.
- Booth FW, Gordon SE, Carlson CJ, Hamilton MT. Waging war on modern chronic diseases: primary prevention through exercise biology. *J Appl Physiol* 2000; **88**: 774–87.
- WAO White Book on Allergy 2011–2012: Executive Summary. Available at: <http://www.worldallergy.org> Latest access date. 2011 Jul 30.
- Walsh NP, Gleeson M, Shephard RJ, et al. Position statement. Part one: immune function and exercise. *Exerc Immunol Rev* 2011; **17**: 6–63.
- Robson PJ, Blannin AK, Walsh NP, Castell LM, Gleeson M. Effects of exercise intensity, duration and recovery on *in vitro* neutrophil function in male athletes. *Int J Sports Med* 1999; **20**: 128–35.
- Peake J, Suzuki K. Neutrophil activation, antioxidant supplements and exercise-induced oxidative stress. *Exerc Immunol Rev* 2004; **10**: 129–41.
- Okutsu M, Suzuki K, Ishijima T, Peake J, Higuchi M. The effects of acute exercise-induced cortisol on CCR2 expression on human monocytes. *Brain Behav Immun* 2008; **22**: 1066–71.
- Ceddia MA, Woods JA. Exercise suppresses macrophage antigen presentation. *J Appl Physiol* 1999; **87**: 2253–8.
- Gleeson M, Bishop NC. The T cell and NK cell immune response to exercise. *Ann Transplant* 2005; **10**: 43–8.

10. Timmons BW, Cieslak T. Human natural killer cell subsets and acute exercise: a brief review. *Exerc Immunol Rev* 2008; **14**: 8–23.
11. Del Giacco SR, Manconi PE, Del Giacco GS. Allergy and sports. *Allergy* 2001; **56**: 215–23.
12. Nieman DC, Pedersen BK. Exercise and immune function. Recent developments. *Sports Med* 1999; **27**: 73–80.
13. Pedersen BK, Hoffmann-Goetz L. Exercise and the immune system: regulation, integration and adaptation. *Physiol Rev* 2000; **80**: 1055–81.
14. Shephard RJ. Adhesion molecules, catecholamines and leucocyte redistribution during and following exercise. *Sports Med* 2003; **33**: 261–84.
15. Bishop NC, Gleeson M. Acute and chronic effects of exercise on markers of mucosal immunity. *Front Biosci* 2009; **14**: 4444–56.
16. Liao HF, Chiang LM, Yen CC, et al. Effect of a periodized exercise training and active recovery program on antitumor activity and development of dendritic cells. *J Sports Med Phys Fitness* 2006; **46**: 307–14.
17. Michishita R, Shono N, Inoue T, Tsuruta T, Node K. Effect of exercise therapy on monocyte and neutrophil counts in overweight women. *Am J Med Sci* 2010; **339**: 152–6.
18. Xepapadaki P, Papadopoulos NG. Childhood asthma and infection: virus-induced exacerbations as determinants and modifiers. *Eur Respir J* 2010; **36**: 438–45.
19. Bonsignore MR, Morici G, Vignola AM, et al. Increased airway inflammatory cells in endurance athletes: what do they mean? *Clin Exp Allergy* 2003; **33**: 14–21.
20. Hashimoto S, Gon Y, Matsumoto K, Takeshita I, Maruoka S, Horie T. Inhalant corticosteroids inhibit hyperosmolarity-induced, and cooling and rewarming-induced interleukin-8 and RANTES production by human bronchial epithelial cells. *Am J Respir Crit Care Med* 2000; **162**: 1075–80.
21. Palange P, Brusasco V, Delgado L, Del Giacco S. Exercise and airway physiology: interactions with immune and allergic responses. In: Carlsen KH, Delgado S, Del Giacco S, eds. *Diagnosis, Prevention and Treatment of Exercise-Related Asthma, Respiratory and Allergic Disorders in Sports*. European Respiratory Society Journals, Sheffield, UK: Maney Publishing, 2005: 10–8.
22. Bougault V, Turmel J, Levesque B, Boulet LP. The respiratory health of swimmers. *Sports Med* 2009; **39**: 295–312.
23. Uyan ZS, Carraro S, Piacentini G, Baraldi E. Swimming pool, respiratory health and childhood asthma: should we change our beliefs? *Pediatr Pulmonol* 2009; **44**: 31–7.
24. Kanazawa H. Microvascular theory of exercise-induced bronchoconstriction in asthma: potential implications of vascular endothelial growth factor. *Inflamm Allergy Drug Targets* 2007; **6**: 133–7.
25. Zietkowski Z, Skiepkowski R, Tomasiak MM, Bodzenta-Lukaszyk A. Endothelin-1 in exhaled breath condensate of allergic asthma patients with exercise-induced bronchoconstriction. *Respir Res* 2007; **8**: 76.
26. Vieira LP, Toledo AC, Ferreira SC, et al. Airway epithelium mediates the anti-inflammatory effects of exercise on asthma. *Respir Physiol Neurobiol* 2011; **175**: 383–9.
27. Hewitt M, Creel A, Estell K, Estell K, Davis IC, Schieberr LM. Acute exercise decreases airway inflammation, but not responsiveness, in an allergic asthma model. *Am J Respir Cell Mol Biol* 2009; **40**: 83–9.
28. Lowder T, Dugger K, Deshane J, Deshane J, Estell K, Schieberr LM. Repeated bouts of aerobic exercise enhance regulatory T cell responses in a murine asthma model. *Brain Behav Immun* 2010; **24**: 153–9.
29. Lodrup Carlsen KC, Haland G, Devulapalli CS, et al. Asthma in every fifth child in Oslo, Norway: a 10-year follow up of a birth cohort study. *Allergy* 2006; **61**: 454–60.
30. Ram FS, Robinson SM, Black PN. Effects of physical training in asthma: a systematic review. *Br J Sports Med* 2000; **34**: 162–7.
31. Counil FP, Varray A, Matecki S, et al. Training of aerobic and anaerobic fitness in children with asthma. *J Pediatr* 2003; **142**: 179–84.
32. Berntsen S, Carlsen KC, Anderssen SA, et al. Norwegian adolescents with asthma are physical active and fit. *Allergy* 2009; **64**: 421–6.
33. Vahlkvist S, Inman MD, Pedersen S. Effect of asthma treatment on fitness, daily activity and body composition in children with asthma. *Allergy* 2010; **65**: 1464–71.
34. Davis KJ, DiSantostefano R, Peden DB. Is Johnny wheezing? Parent-child agreement in the childhood asthma in America survey. *Pediatr Allergy Immunol* 2011; **22**: 31–5.
35. Deal EC Jr, McFadden ER Jr, Ingram RH Jr, Strauss RH, Jaeger JJ. Role of respiratory heat exchange in production of exercise-induced asthma. *J Appl Physiol* 1979; **46**: 467–75.
36. Anderson SD, Daviskas E. The mechanism of exercise-induced asthma is. *J Allergy Clin Immunol* 2000; **106**: 453–9.
37. Carlsen KH, Engh G, Mørk M. Exercise induced bronchoconstriction depends on exercise load. *Respir Med* 2000; **94**: 750–5.
38. Anderson SD, Charlton B, Weiler JM, Nichols S, Spector SL, Pearlman DS. Comparison of mannitol and methacholine to predict exercise-induced bronchoconstriction and a clinical diagnosis of asthma. *Respir Res* 2009; **10**: 4.
39. Refsum HE, Fönstelién E, Oseid S, Edwards AM. Exercise-associated ventilatory insufficiency in adolescent athletes. In: Oseid S, Edwards AM, eds. *The Asthmatic Child in Play and Sports*. London: Pitmann Books Limited, 1983: 128–39.
40. Kenn K, Balkissoon R. Vocal cord dysfunction: what do we know? *Eur Respir J* [Review] 2011; **37**: 194–200.
41. Heimdal JH, Roksund OD, Halvorsen T, Skadberg BT, Olofsson J. Continuous laryngoscopy exercise test: a method for visualizing laryngeal dysfunction during exercise. *Laryngoscope* 2006; **116**: 52–7.
42. Henriksen JM, Dahl R. Effects of inhaled budesonide alone and in combination with low-dose terbutaline in children with exercise-induced asthma. *Am Rev Respir Dis* 1983; **128**: 993–7.
43. Carlsen KH, Røksund O, Olsholt K, Njū F, Leegaard J, Bratten G. Overnight protection by inhaled salmeterol on exercise-induced asthma in children. *Eur Respir J* 1995; **8**: 1852–5.
44. Knopfli BH, Bar-Or O. Vagal activity and airway response to ipratropium bromide before and after exercise in ambient and cold conditions in healthy cross-country runners. *Clin J Sport Med* 1999; **9**: 170–6.
45. Subbarao P, Duong M, Adelroth E, et al. Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma. *J Allergy Clin Immunol* 2006; **117**: 1008–13.
46. Carlsen KH. The breathless adolescent asthmatic athlete. *Eur Respir J* 2011; **38**: 713–20.
47. Bougault V, Turmel J, St-Laurent J, Bertrand M, Boulet LP. Asthma, airway inflammation, and epithelial damage in swimmers and cold-air athletes. *Eur Respir J* 2009; **33**: 740–6.
48. Stadelmann K, Stensrud T, Carlsen KH. Respiratory symptoms and bronchial responsiveness in competitive swimmers. *Med Sci Sports Exerc* 2011; **43**: 375–81.
49. Arvaniti F, Piftis KN, Papadimitriou A, et al. Adherence to the Mediterranean type of diet is associated with lower prevalence of asthma symptoms, among 10–12 years old children: the PANACEA study. *Pediatr Allergy Immunol* 2011; **22**: 283–9.
50. Bueso AK, Berntsen S, Mowinkel P, Andersen LF, Lodrup Carlsen KC, Carlsen KH. Dietary intake in adolescents with asthma – potential for improvement. *Pediatr Allergy Immunol* 2011; **22**: 19–24.
51. Hompes S, Kohli A, Nemat K, et al. Provoking allergens and treatment of anaphylaxis in children and adolescents – data from the anaphylaxis registry of

- German-speaking countries. *Pediatr Allergy Immunol* 2011; **22**: 568–74.
52. Moro MM, Tejedor Alonso MA, Esteban HJ, Mugica Garcia MV, Rosado IA, Vila AC. Incidence of anaphylaxis and subtypes of anaphylaxis in a general hospital emergency department. *J Invest Allergol Clin Immunol* 2011; **21**: 142–9.
 53. Wolanczyk-Medrała A, Barg W, Radlinska A, Panaszek B, Medrała W. Food-dependent exercise-induced anaphylaxis—sequence of causative factors might be reversed. *Ann Agric Environ Med* 2010; **17**: 315–7.
 54. Du TG. Food-dependent exercise-induced anaphylaxis in childhood. *Pediatr Allergy Immunol* 2007; **18**: 455–63.
 55. Barg W, Medrała W, Wolanczyk-Medrała A. Exercise-induced anaphylaxis: an update on diagnosis and treatment. *Curr Allergy Asthma Rep* 2011; **11**: 45–51.
 56. Robson-Ansley P, Toit GD. Pathophysiology, diagnosis and management of exercise-induced anaphylaxis. *Curr Opin Allergy Clin Immunol* 2010; **10**: 312–7.
 57. Castells MC, Horan RF, Sheffer AL. Exercise-induced anaphylaxis. *Curr Allergy Asthma Rep* 2003; **3**: 15–21.
 58. Katelaris CH. Allergy and athletes. *Curr Allergy Asthma Rep* 2001; **1**: 397–8.
 59. Calvani M, Sopo SM. Exercise-induced anaphylaxis caused by wheat during specific oral tolerance induction. *Ann Allergy Asthma Immunol* 2007; **98**: 98–9.
 60. Varshney P, Steele PH, Vickery BP, et al. Adverse reactions during peanut oral immunotherapy home dosing. *J Allergy Clin Immunol* 2009; **124**: 1351–2.
 61. Barg W, Wolanczyk-Medrała A, Obojski A, Wytrychowski K, Panaszek B, Medrała W. Food-dependent exercise-induced anaphylaxis: possible impact of increased basophil histamine releasability in hyperosmolar conditions. *J Invest Allergol Clin Immunol* 2008; **18**: 312–5.
 62. Popowski LA, Oppliger RA, Patrick LG, Johnson RF, Kim JA, Gisolf CV. Blood and urinary measures of hydration status during progressive acute dehydration. *Med Sci Sports Exerc* 2001; **33**: 747–53.
 63. Azofra GJ, Sastre DJ, Olaguibel Rivera JM, Hernandez de RD, Estupinan SM, Sastre CA. Exercise-induced anaphylaxis: inhibition with sodium bicarbonate. *Allergy* 1986; **41**: 471.
 64. Saeki K, Endo K, Yamasaki H. Histamine release by inorganic cations from mast cell granules isolated by different procedures. *Jpn J Pharmacol* 1972; **22**: 27–32.
 65. Hultman E, Sahlin K. Acid-base balance during exercise. *Exerc Sport Sci Rev* 1980; **8**: 41–128.
 66. Matsuo H, Morimoto K, Akaki T, et al. Exercise and aspirin increase levels of circulating gliadin peptides in patients with wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy* 2005; **35**: 461–6.
 67. van Nieuwenhoven MA, Brouns F, Brummer RJ. The effect of physical exercise on parameters of gastrointestinal function. *Neurogastroenterol Motil* 1999; **11**: 431–9.
 68. Palosuo K, Varjonen E, Nurkkala J, et al. Transglutaminase-mediated cross-linking of a peptic fraction of omega-5 gliadin enhances IgE reactivity in wheat-dependent, exercise-induced anaphylaxis. *J Allergy Clin Immunol* 2003; **111**: 1386–92.
 69. Galli SJ. New concepts about the mast cell. *N Engl J Med* 1993; **328**: 257–65.
 70. Vatner SF, Pagani M. Cardiovascular adjustments to exercise: hemodynamics and mechanisms. *Prog Cardiovasc Dis* 1976; **19**: 91–108.
 71. Commins SP, Satinover SM, Hosen J, et al. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose- α -1,3-galactose. *J Allergy Clin Immunol* 2009; **123**: 426–33.
 72. Palosuo K, Varjonen E, Kekki OM, et al. Wheat omega-5 gliadin is a major allergen in children with immediate allergy to ingested wheat. *J Allergy Clin Immunol* 2001; **108**: 634–8.
 73. Nakamizo S, Egawa G, Miyachi Y, Kabashima K. Cholinergic urticaria: pathogenesis-based categorization and its treatment options. *J Eur Acad Dermatol Venereol* 2012; **26**: 114–6.